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A cross-sectional national questionnaire survey assessing the clinical attitudes of members of the British Menopause Society to the management of women with premature ovarian insufficiency

Monica Mittal[1], Michael Savvas[1], Nitish Narvekar[1], Nick Panay[2] and Haitham Hamoda[1]

Abstract

Objective: To explore the current clinical attitudes of members of the British Menopause Society to the management of premature ovarian insufficiency.

Design: An electronic cross-sectional questionnaire survey.

Setting: Members of the British Menopause Society.

Population: All members of the British Menopause Society with a valid email address.

Method: Completion of an electronic survey.

Main outcome measures: Investigations and treatment options and preferences for the management of women with premature ovarian insufficiency.

Results: A total of 130 questionnaires were returned and analysed. The majority of responses were from Hospital Consultants ($n = 55/130$; 42.3%). A total of 53/124 (42.7%) clinicians routinely performed a bone density scan. A total of 73/130 (56.2%) clinicians would prescribe hormone replacement therapy in preference to combined ethinyl estradiol and progesterone (COC; 27/130, 20.8%). A total of 44/108 (40.7%) routinely prescribed oral estradiol in preference to transdermal administration (62/108, 57.4%). A total of 26/128 (20.3%) prescribed oral micronised progesterone, 31/128 (24.2%) oral progestogens, while 42/128 (32.8%) preferred the intra-uterine system. Fertility concerns remain an important aspect of care, with 33.9% ($n = 39/115$) of clinicians indicating that more than 50% of their patients had a concern regarding their fertility.

Conclusion: The majority of clinicians indicated a preference for hormone replacement therapy instead of the COC as their choice of hormone replacement in women with premature ovarian insufficiency. However, there was a significant variation in practices. This information can be useful in counselling women and in guiding clinical practitioners. The results highlight the need for further research to determine the optimal regimens for the management of women with premature ovarian insufficiency.

Keywords

Estrogen, hormone replacement therapy, menopause, osteoporosis, vasomotor symptoms

Introduction

Premature ovarian insufficiency (POI) was first described in 1942 by Albright et al.[1] POI generally describes a syndrome associated with amenorrhoea of at least four months duration, hypo-estrogenism and raised gonadotropin levels.[2] Definitive criteria for the diagnosis of the condition have not yet been established, and this has resulted in varied

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approaches to the management of this condition amongst practitioners. It is estimated to affect 1% of women under 40 years of age.[2] The syndrome can have both devastating short- and long-term consequences for the affected patient population secondary to the deficiency of sex steroids, namely climacteric symptoms,[3–5] osteoporosis,[3–6] cardiovascular disease[3,5–7] and subfertility.[3–7]

It has been reported that approximately 50% of women have described their experience at the time of the initial diagnosis as being unsatisfactory, citing a delay in receiving a diagnosis and feeling a lack of available support.[8]

There is lack of evidence from randomised trials to guide practice, and the optimal management of the condition remains largely unanswered, with considerable variation in practices amongst clinicians. The objective of this survey was to explore the current attitudes of members of the British Menopause Society (BMS) to the management of women with POI.

Methods

An electronic cross-sectional questionnaire survey was distributed to members of the BMS by email through the BMS. The objective was to assess the views and approaches of practitioners with a special interest in this field to the management of women with POI. The survey assessed the investigations and treatment options more commonly recommended to help standardise practices. The survey assessed the grade and location of practice of the respondents, and the source of referral of the patients. It also addressed the views of the practitioners on the investigation and management of women with POI. The questions assessed are summarised in Table 1. The data were analysed

Table 1. Questions assessed in the survey with answer options.

Question	Answer options
Do you carry out a bone density scan on women with POI?	Yes – routinely/yes – selectively/no
Do you carry out a karyotype analysis on women with POI?	Yes – routinely/yes – selectively/no
Do you carry out an autoantibody screen on women with POI?	Yes – routinely/yes – selectively/no
What is your preferred choice of hormonal treatment for the management of women with POI?	Combined synthetic estrogen and progestogen/HRT sequential/HRT continuous combined
What is your preferred brand of hormone replacement therapy that you usually prescribe for women with POI?	Free text answer
What proportion of your patients, choose to use the combined oral contraceptive pill?	<25% / 25–50% / >50%
What is your preferred route for estrogen administration when prescribing hormone replacement therapy?	Oral/transdermal-patch/transdermal-gel/implant
What is your preferred progesterone preparation when prescribing hormone replacement therapy?	Micronised progesterone/oral progestogens/transdermal progestogens/intra-uterine progestogens-Mirena intra-uterine system
Do you routinely counsel patients about testosterone replacement?	Yes/no
What proportion of your patients, have testosterone replacement?	<25% / 25–50% / >50%
Approximately what percentage of your patients, choose not to take hormone replacement?	<25% / 25–50% / >50%
What percentage of your patients, express concerns regarding their fertility?	<25% / 25–50% / >50%
Who are these patients routinely followed up by?	General practitioner/hospital consultant/specialist gynaecology nurse/other
Do you think that these patients should be managed in primary or secondary care?	Primary care/secondary care
Until what age do you counsel your patients with premature ovarian insufficiency to continue taking hormone replacement therapy?	Free text answer

POI: premature ovarian insufficiency.

using the Statistical Package for Social Sciences (SPSS Version 17.0).

Results

An electronic questionnaire was sent to all members of the BMS who had provided a contact email address. A total of 130/300 (43.3%) questionnaires were returned and all of these were analysed and included in the study. The denominators vary according to the number of responses to the individual questions. Hospital consultants constituted 42.3% ($n = 55/130$) of the responses. General practitioners (GP) and Associate Specialists/Specialist Registrars each accounted for 16.2% ($n = 21/130$) of responses, the remainder were Community Gynaecology Consultants ($n = 3/130$; 2.3%), Consultants in the private sector ($n = 2/130$; 1.5%) and Specialist Nurses ($n = 7/130$; 5.3%); 16.2% ($n = 21/130$) of respondents did not specify their grade or place of practice.

A total of 96/127 (75.6%) referrals were from GPs; 16/127 (12.6%) from other hospital specialities including general gynaecology clinics, subfertility clinics and oncology departments, while 15 (11.8%) respondents did not specify the source of their referrals.

Clinicians' practices and views on investigations that are considered part of the management of women with POI are shown in Table 2. Bone densitometry scans were repeated at varied intervals by different clinicians; 16.4% ($n = 20/122$) would repeat them every 1–3 years compared to an equal number of clinicians ($n = 45/122$; 36.9%) who would repeat them every 3–5 years or not routinely repeat them at all. 9.8% ($n = 12/122$) of clinicians did not specify.

The hormone treatment preferences of clinicians for women with POI are summarised in Table 3, and clinicians' perceptions of their patients' views on treatment are shown in Table 4, while respondents' preferred brands of hormone replacement therapy (HRT) for women with POI are shown in Figure 1.

A total of 44/108 (40.7%) respondents indicated that the oral route was their preferred route for administration of estrogen, while for 62/108 (57.4%) it was the transdermal route (patch or gel). Of the latter, 46/62 (74%) preferred patches whilst 16/62 (26%) preferred the gel. A total of 26/128 (20.3%) clinicians answered that oral micronised progesterone was their preferred progesterone; 31/128 (24.2%) preferred oral progestogens, 42/128 (32.8%) answered 'intra-uterine progestogens', while 10/128 (7.8%) were in preference of transdermal progestogen administration. In all, 14.8% ($n = 19/128$) did not specify.

A total of 52.2% ($n = 59/113$) of clinicians indicated that they would counsel their patients regarding concomitant testosterone replacement therapy, with 47.8% ($n = 54/113$) not routinely counselling their patients.

A total of 88.4% ($n = 100/113$) of clinicians counselled their patients to continue hormone replacement at least until the average age of the menopause (age 52 years). The age ranges across which clinicians advise continuing hormone replacement up until are shown in Figure 2.

A total of 66/129 (51.2%) clinicians reported that their patients would be followed up by their GP,

Table 2. Clinicians' practices and views on investigations that may be considered part of the management of women with POI.

	Total *n* (%)	95% CI[a] (%)
Do all new cases diagnosed with POI undergo: DEXA scan?		
Yes – routinely	53/124 (42.7)	34 to 52
Yes – selectively	39/124 (31.5)	24 to 40
No	32/124 (25.8)	19 to 34
Karyotype analysis?		
Yes – routinely	20/123 (16.3)	11 to 24
Yes – selectively	71/123 (57.7)	49 to 66
No	32/123 (26.0)	17 to 37
Autoantibody screen?		
Yes – routinely	41/117 (35.0)	27 to 44
Yes – selectively	36/117 (30.8)	23 to 40
No	40/117 (34.2)	26 to 43

[a]95% CI: 95% confidence interval for the proportions.
POI: premature ovarian insufficiency.

Table 3. Hormone treatment preferences of clinicians for women with POI.

	Total *n* (%)	95% CI[a] (%)
Combined synthetic estrogen and progesterone	27/130 (20.8)	15 to 29
Hormone replacement therapy	73/130 (56.2)	48 to 64
HRT – sequential combined	41/130 (31.5)	24 to 40
HRT – continuous combined	32/130 (24.6)	18 to 33
Other	30/130 (23.1)	17 to 31

[a]95% CI: 95% confidence interval for the proportion.
HRT: hormone replacement therapy.

Table 4. Clinicians' perception of their patients' views on treatment.

	<25% of patients, *n* (%)	25–50% of patients, *n* (%)	>50% of patients, *n* (%)	Did not specify, *n* (%)
Proportion of patients opting to use the COCP	68/122 (55.7)	0/122 (0)	19/122 (15.6)	35/122 (28.7)
Proportion of patients choosing not to take any form of hormonal replacement	98/120 (81.7)	12/120 (10)	5/120 (4.2)	5/120 (4.2)
Uptake of testosterone replacement therapy	87/117 (74.4)	19/117 (16.2)	5/117 (4.3)	6/117 (5.1)
Proportion of patients expressing concerns regarding fertility	24/115 (20.9)	49/115 (42.6)	39/115 (33.9)	3/115 (2.6)

COCP: combined oral contraceptive pill.

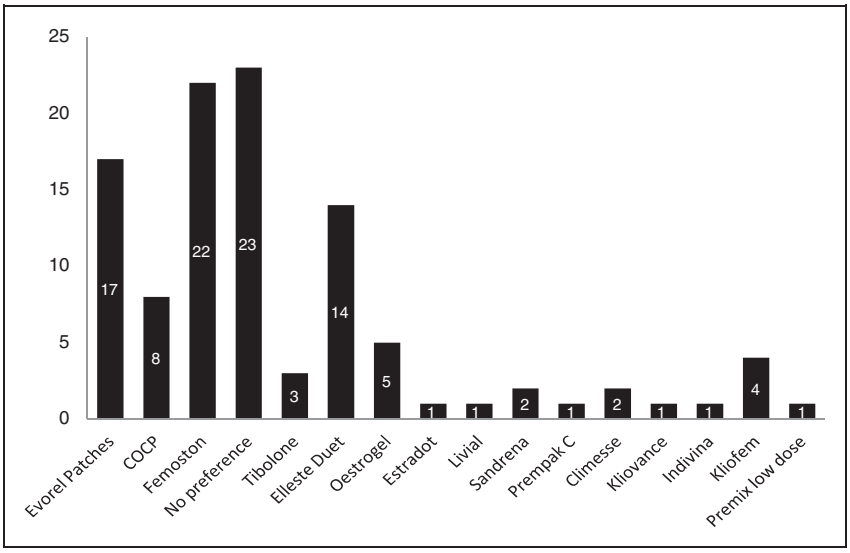

Figure 1. Respondents preferred brand of HRT for women with POI. No preference 21.7% ($n = 23/106$); Femoston 20.8% ($n = 22/106$); Evorel patches 16.0% ($n = 17/106$); Elleste Duet 13.2% ($n = 14/106$); COCP 7.5% ($n = 8/106$); Oestrogel 5.0% ($n = 5/106$); Kliofem 3.8% ($n = 4/106$); Tibolone 2.8% ($n = 3/106$); Sandrena 1.9% ($n = 2/106$); Climesse 1.9% ($n = 2/106$); Kliovance 0.9% ($n = 1/106$); Indivina 0.9% ($n = 1/106$); Prempak C 0.9% ($n = 1/106$); Estradot 0.9% ($n = 1/106$); Livial 0.9% ($n = 1/106$); Premique low dose 0.9% ($n = 1/106$).

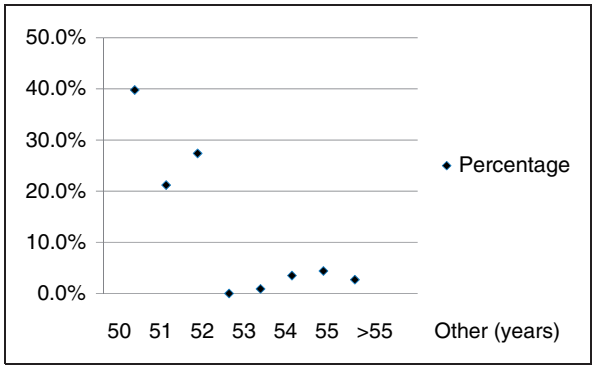

Figure 2. The age ranges across which clinicians advise continuing hormone replacement up until: 50 years of age – $n = 45/113$, 39.8%; 51 years of age – $n = 24/113$, 21.2%; 52 years of age – $n = 31/113$, 27.4%; 53 years of age – $n = 0/113$, 0%; 54 years of age – $n = 1/113$, 0.9%; 55 years of age – $n = 4/113$, 3.5%; >55 years of age – $n = 5/113$, 4.4%; other – $n = 3/113$, 2.7%.

53/129 (41.1%) of clinicians arranged follow-up within a hospital setting while 4/129 (3.1%) reported follow-up with the Specialist Gynaecology Nurses. A total of 6/129 (4.7%) clinicians did not specify. When specifically questioned about whether these patients should be followed up in primary or secondary care settings, the responses were 47.3% ($n = 53/112$) and 52.7% ($n = 59/112$), respectively.

33.9% ($n = 39/115$) of clinicians reported that more than 50% of their population expressed concerns regarding their fertility, with 42.6% ($n = 49/115$) reporting that 25–50% of their patients' had fertility concerns while 20.9% ($n = 24/115$) of respondents estimated that less than 25% of their patient population had concerns regarding their fertility.

Discussion

This national questionnaire survey assessed the attitudes of members of the BMS to the management of women with POI. The responses in the survey showed a varied approach to the assessment and management of women presenting with this condition.

Main findings

Over half the respondents indicated that HRT was their preferred means of hormone replacement, while a fifth had the combined oral contraceptive pill (COCP) as their preferred option. Of the former group, the majority indicated a preference for transdermal over oral preparations. A quarter of practitioners mentioned they did not carry out a bone density scan as part of their management, while half did not routinely counsel their women about testosterone replacement. The majority recommended continuation of hormone replacement until the average age of the natural menopause.

Strengths and limitations

This survey, despite being a subjective analysis of current clinical practices, provides a view of the current trends of management of women with POI within the United Kingdom. The survey assessed the main aspects involved in the management of women with POI as highlighted in previously published literature on this topic,[2,9] and included the views of practitioners' who are specialists or had a special interest in this field.

Interpretation

Studies have shown that women with POI have a higher incidence of ischaemic heart disease (IHD), mortality secondary to IHD and an increased overall mortality.[10,11] Women with POI have also been shown to have reduced bone mineral density (BMD) and an increased incidence of fractures compared to controls.[12] Estrogen replacement has been shown in observational studies to lower the risks of cardiovascular disease, osteoporosis and fractures. Most international guidance documents recommend continuing hormone replacement until the natural age of the menopause.[13–15] However, there is lack of data from randomised controlled trials (RCTs) to demonstrate the benefits of the various treatment regimens and this may explain the large variations noted amongst practitioners. More research is required to further assess this and guide clinical practice.[10,11]

Vega et al.,[16] reported on the loss of bone mass and the risk of fractures in relation to the age of onset of the menopause. Women who suffered an early menopause had significantly lower spinal bone density (4%) compared to controls and femoral neck bone density (7%), as well as a threefold higher incidence of hip fractures by the age of 66 years (9.4% for early menopause compared with 3.3% in woman who had a normal menopause and none in the late menopause group).

Gallagher[12] reported a summary of the published literature on the risk of bone loss and fractures in women with early menopause. The review included large well-designed observational studies, and concluded that an early menopause, usually before age 45 years, leads to a higher risk of osteoporosis and a higher incidence of fractures, while a reduction in the incidence of fractures was noted with the use of hormonal therapy. The author concluded that women who experience an early menopause at an age younger than 45 years should undergo BMD measurements within 10 years of the menopause as the evidence indicates a higher incidence of serious osteoporotic

fractures such as spinal and hip fractures in this group. In this survey, we noted a varied approach among respondents to carrying out BMD assessments in women with POI, with a third indicating that they only carried it out selectively, while a quarter indicated that they did not carry it out at all. It can be argued that women taking adequate HRT until the average age of the menopause, specifically those in whom treatment is commenced early, will be at lower risk of having low bone density, and this may partly explain some of the varied practices seen regarding the performance of bone density assessment. Furthermore, access to bone density assessment may not be readily available to all practitioners looking after women with POI. In contrast, in women with untreated POI, BMD assessment can act as a tool in emphasising the benefits of HRT.

The women's health initiative study revealed an overall increased incidence of stroke in women who commenced oral estrogen and progestogen therapy or oral estrogen alone between the ages of 50 and 79 years. This risk was age related and was noted to be lower in women between ages 50 and 59 years.[17,18] These data should, however, not be extrapolated to include women with POI, as this group represents a different cohort with a different pathophysiology. A review of seven observational studies showed an increased risk of all stroke including ischaemic stroke in women who underwent an early menopause before the age of 50 years, with the risk reduced in women who received hormone therapy.[19]

All routes of estrogen administration can effectively treat menopausal symptoms and provide cardiovascular and bone protection in women with POI. However, the different routes of administration follow different metabolic pathways and as a result can have different advantages and disadvantages. Oral estrogen administration follows a first-pass hepatic metabolism pathway and this can adversely affect the coagulation cascade and pro-inflammatory markers, including C-reactive protein, compared to transdermal administration. There is a lack of evidence assessing the effects of the route of estradiol administration in women with POI. Two large nested case–controlled studies that reviewed the UK's General Practice Research Database have shown a reduced risk of stroke and venous thrombosis in naturally menopausal women between the ages of 50 and 79 years receiving transdermal estradiol compared to oral preparations.[20,21] These findings cannot be extrapolated to include women with POI, and further research is needed to assess this effect in women with POI. In our survey, it was noted that the majority of practitioners had a preference for transdermal estradiol administration over the oral route. More research is needed to determine the optimal regimen and route of HRT administration in women with POI. The views assessed in our survey were those of the clinicians looking after women with POI. The choice of hormonal therapy being HRT or the COCP, and route of administration, however, will ultimately be decided by the woman's preferences, contraceptive and fertility needs, but is likely to be influenced by the advice and guidance provided by their supervising practitioner.

Micronised progesterone has also been shown to have a better safety profile when compared to its synthetic counterparts. Observational studies in women beyond the natural age of the menopause have reported a lower risk of breast cancer compared with synthetic progestogens,[22] in addition to having a neutral effect on the vasculature and therefore, a lower risk of venous thromboembolic disease and cardiovascular disease compared with synthetic progestogens.[23] There is a lack of evidence on the effect of various progesterone preparations in women with POI. Our survey showed that approximately a fifth of practitioners preferred micronised progesterone while the majority showed a preference for synthetic progestogens. A currently ongoing RCT is assessing the cardiovascular effects, effects on lipid and coagulation profiles of micronised progesterone versus medroxyprogesterone acetate in combination with transdermal estradiol in women with POI.[24]

Panay et al.[25] reported a questionnaire survey that assessed UK and international practices on the management of POI. The survey included 50 health professionals and reported varied practices in both diagnosis and management. Various terminologies were used with 54% using premature ovarian failure, 16% using POI and 14% primary ovarian dysfunction. 48% routinely carried out BMD assessment at diagnosis. 92% indicated they would use HRT while 68% would consider the COCP, the latter being more common in the UK than elsewhere. UK practitioners were more likely to use transdermal HRT compared to European practitioners and the majority recommended continuation of therapy until the natural age of the menopause. The authors concluded that there was little consensus on nomenclature with much geographic variations in clinical practice particularly with the route of estrogen replacement.

Rebar and Connolly[26] reported that 55% of women with POI and primary amenorrhoea were noted to have chromosomal abnormalities compared to 13% of women with secondary amenorrhoea who developed POI before the age of 30 years. It has been reported that 10–20% of women with POI have some evidence of autoimmunity with thyroid autoimmune disorders being the commonest. However, the pathogenic role of anti-ovarian antibodies in POI remains questionable. In this survey, approximately three quarters of practitioners indicated that they would carry out karyotype

analysis either routinely or selectively on women with POI, a third indicated they would routinely perform an autoantibody screen, a third did it selectively while a further third would not perform an autoantibody screen, again showing little consensus among practitioners.[27,28]

In this survey, future fertility potential was reported by clinicians to be a major concern for a significant proportion of their patient population. Being faced with an early menopause can be a devastating event and a life altering diagnosis for many women. Spontaneous ovulation may occur sporadically and it has been reported that 5–10% of women with POI conceive at sometime after the diagnosis. However, assisted reproductive techniques with donated oocytes remains the most realistic means to achieve a pregnancy in women with POI.[28] With such a high percentage of women expressing concerns regarding their fertility, recourse to counselling and fertility clinics offering egg donation treatment becomes important. A multidisciplinary approach to the management of these women will enable these aspects of care to be addressed.

Conclusion

This survey has shown a significant variation in the approach to the management of women with POI. This information can be useful in counselling women and in guiding clinical practitioners. The results highlight the need for further research to determine the optimal regimens for the management of women with POI and the call for a national registry database and national guidelines to inform clinical practice.

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Conflict of interest

None declared.

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